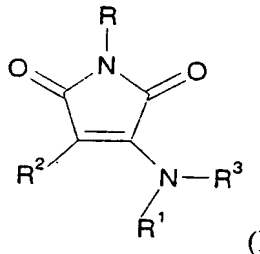
Claims

1. A method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, dementias such as Alzheimer's disease and manic depression which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof, wherein:

R is hydrogen, alkyl, aryl, or aralkyl;

R^1 is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;

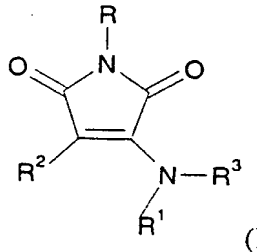
R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;

R^3 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocylic ring;

to a human or non-human mammal in need thereof.

2. A compound of formula (IB),



(IB)

or a derivative thereof, wherein:

R is hydrogen, alkyl, aryl, or aralkyl;

R^1 is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;

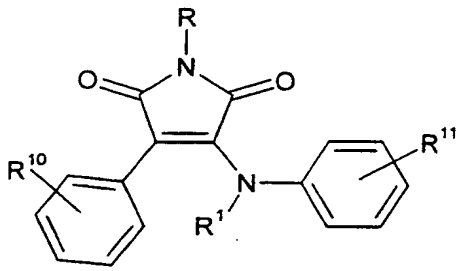
R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;

R^3 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

contd. a1

R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocylic ring;
with the proviso that formula (IB) does not include the compounds contained in List B.

3. A compound according to claim 2 of formula (IC')



(IC')

wherein;

R and R^1 are as defined in relation to formula (I) in claim 1;

R^{10} represents hydrogen or one or more substituents, suitably up to three, selected from the list consisting of: alkoxycarbonyl, alkoxyalkyl, perfluoroalkyl, perfluoroalkylS-, perfluoroalkylO-, phenyl(di-C_{1-6}alkoxy)C-, benzoyl, C_{1-6}alkylSO_2-, -[(CH=CH)$_2$]-, phenyl, nitro, -OCH_2O-, benzyloxy, phenoxy, halo, hydroxy, alkyl, alkoxy, amino, mono- or di-alkyl amino or thioalkyl;

R^{11} represents hydrogen or one or more substituents, suitably up to three, selected from the list consisting of: substituted or unsubstituted C_{1-6}alkyl, phenyl, benzyl, substituted or unsubstituted C_{1-6}alkylS-, halo, hydroxy, substituted or unsubstituted C_{1-6}alkoxy, substituted or unsubstituted phenoxy, indolyl, naphthyl, carboxy, C_{1-6}alkoxycarbonyl, benzyloxy, phenoxy, pentafluorophenoxy, nitro, substituted or unsubstituted carbamoyl, substituted or unsubstituted C_{1-6}alkylcarbonyl, benzoyl, cyano, perfluoroC_{1-6}alkylSO_2-, C_{1-6}alkylNHSO_2-, oxazolyl, substituted or unsubstituted phenylS-, C_{1-6}alkylpiperazinyl-, C_{1-6}alkylcarbonylpiperazinyl-, 1,2,3-thiadiazolyl, pyrimidin-2-yloxy, N-[pyrimidin-2-yl]-N-methylamino, phenylamino, C_{1-6}alkylsulphonylamino, N-morpholinylcarbonyl, cyclohexyl, adamantyl, trityl, substituted or unsubstituted C_{1-6}alkenyl, perfluoroC_{1-6}alkyl, perfluoroC_{1-6}alkoxy, perfluoroC_{1-6}alkylS-, aminosulphonyl, morpholino, (diC_{1-6}alkyl)amino, C_{1-6}alkylCONH-, (diC_{1-6}alkoxy)phenyl$(CH_2)_n$NHC(O)CH(phenyl)S- where n is 1 to 6, and C_{1-6}alkylCON(C_{1-6}alkyl)-, thiazolidinedionylC_{1-6}alkyl, phenylCH(OH)-, substituted or unsubstituted piperazinylC_{1-6}alkoxy, substituted or unsubstituted benzoylamino;
or -$(CH_2)_x$-, -SCH=N-, -SC(C_{1-6}alkyl)=N-, -OCF_2O-, -[CH=CHC(O)O]-, -[N=CH-CH=CH]-, -CH=N-NH-, -CH=CH-NH-, -OC(NHC_{1-6}alkyl)=N-, -OC(O)NH-, -C(O)NMeC(O)-, -C(O)NHC(O)-, -$(CH_2)_x$C(O)-, -N=N-NH-, -N=C(C_{1-6}alkyl)O-, -$O(CH_2)_xO$-, -$(CH_2)_xSO_2(CH_2)_y$-,
and -N(C_{1-6}alkylcarbonyl)$(CH_2)_x$-, where x and y are independently 1 to 4;
with the proviso that (IC') does not include:
3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione;

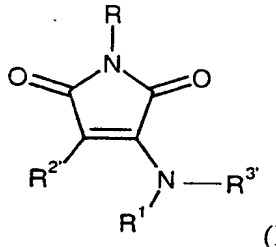
contd. A1

~~1-(4-methylphenyl)-3-[(4-methylphenyl)amino]-4-phenyl-1H-pyrrole-2,5-dione;~~
3-(4-methylphenyl)-1-phenyl-4-(phenylamino)-1H-pyrrole-2,5-dione;
1,3-bis(4-methylphenyl)-4-[(4-methylphenyl)amino]-1H-yrrole-2,5-dione, or;
3-(4-nitrophenyl)-1-phenyl-4-phenylamino-1H-pyrrole-2,5-dione.

4. A compound according to claim 3 wherein
R and R^1 each represent hydrogen, and;
R^{10} and R^{11} are defined as follows:
when R^{10} is 4-Cl, then R^{11} is 3-Cl, 3-Br, or 4-CH_2SO_2NHMe;
when R^{10} is 2-OMe, then R^{11} is 4-OMe or 3,5-di-F;
when R^{10} is 2-F, then R^{11} is 3,5-di-F;
when R^{10} is 3-F, then R^{11} is 4-$(CH_2)_3CO_2H$;
when R^{10} is 2,3-di-F-Ph, then R^{11}1 is 3,5-di-F.

Amen. A2

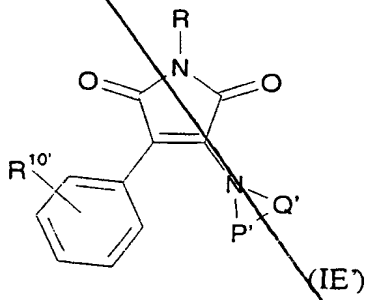
5. A compound according to claim 2 of formula (ID')



(ID')

wherein R and R^1 are as defined in relation to formula (I) in claim 1;
$R^{2'}$ is phenyl, substituted phenyl or indolyl;
$R^{3'}$ is hydrogen, alkyl, cycloalkyl, phenyl, substituted phenyl, C_{1-6} alkylphenyl wherein the phenyl group is optionally substituted, alkoxyalkyl, substituted or unsubstituted heterocyclyl, with the proviso that formula (ID') does not include the compounds contained in List D'.

6. A compound according to claim 2 of formula (IE')



(IE')

wherein R is as defined in relation to formula (I) in claim 1;

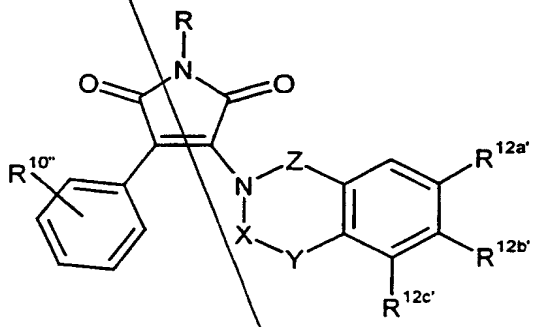
contd. a2

$R^{10'}$ represents hydrogen or one or more, suitably up to three, substituents selected from the list consisting of: alkoxy, halo, and nitro;

P'-Q' represents $-(CH_2)_aO(CH_2)_b-$, $-(CH_2)_aS(CH_2)_b-$, $-(CH_2)_c-$, $-(CH_2)_dCH(G)(CH_2)_e-$, $-(CH_2)_aN(ZZ)(CH_2)_b-$, where a, b, d, and e are independently 1 to 4, c is 1 to 6, ZZ is hydrogen, alkyl, aryl, or alkylcarbonyl, and G is alkyl, amido, hydroxyalkyl, aralkyl, or hydroxy, with the proviso that (IE') does not include:

3-phenyl-4-piperidin-1-yl-pyrrole-2,5-dione;
3-(4-methylpiperazin-1-yl)-4-phenyl-pyrrole-2,5-dione;
3-(4-ethylpiperazin-1-yl)-4-phenyl-pyrrole-2,5-dione;
3-(4-chlorophenyl)-4-(4-methyl-piperazin-1-yl)-pyrrole-2,5-dione;
3-(4-methylphenyl)-4-(4-morpholinyl)-1-phenyl-1H-pyrrole-2,5-dione
3-phenyl-4-(4-methylpiperazino)-pyrrole-2,5-dione;
3-phenyl-4-(4-phenylpiperazino)-pyrrole-2,5-dione;
1-methyl-3-phenyl-4-(4-phenylpiperazino)-pyrrole-2,5-dione;
1-ethyl-3-phenyl-4-(4-chlorophenylpiperazino)-pyrrole-2,5-dione;
1-allyl-3-phenyl-4-(4-methylpiperazino)-pyrrole-2,5-dione, and;
1,3-diphenyl-4-piperidino-pyrrole-2,5-dione.

7. A compound according to claim 2 of formula (IF)



(IF)

wherein R is as defined in relation to formula (I) in claim 1;

R10" is one or more, suitably up to three, substituents selected from the list consisting of perfluoroalkyl, halo, nitro, alkoxy, arylcarbonyl, alkyl;

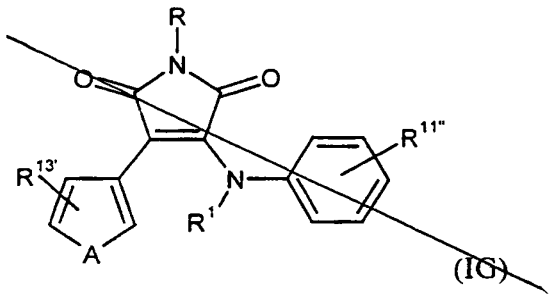
Z is a bond or an alkylene chain;

-X-Y- is –CH=N, $-(CH_2)_t-$, $-(CH_2)_uCH(U)-$, $-(U)CH(CH_2)_u-$, -CH=CH-, $-(CH_2)_vC(alkyl)_2-$, $-C(O)C(alkyl)_2-$, -C(O)O-, where t, u, and v are independently 1 to 4, and U is alkyl, carboxy, alkoxycarbonyl, hydroxyalkyl, and amido;

$R^{12a'}$, $R^{12b'}$, and $R^{12c'}$ are each independently hydrogen, nitro, alkoxy, 4-ethylpiperazin-1-yl, 4-BOC-piperazin-1-yl, 4-methyl-piperazin-1-yl, 4-methyl-piperazin-1-yl, halo, alkyl, piperazin-1-yl, perfluoroalkyl, and alkylsulphonylamino.

8. A compound according to claim 2 of formula (IG)

contd.
a2



(IG)

wherein R and R^1 are as defined in relation to formula (I) in claim 1;

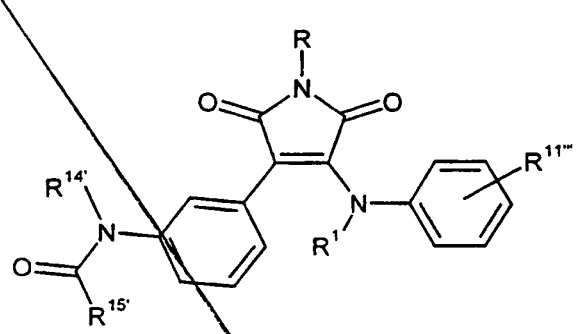
A is N(alkyl), oxygen, or sulphur.

Examples of A are N(methyl), oxygen, and sulphur.

Preferably, A is sulphur.

$R^{11"}$ is one or more, suitably up to three, substituents selected from the group consisting of hydrogen, halo, alkyl, alkylthio, -S-CH=N-, phenoxy, $-(CH_2)_w-$, hydroxy, carboxy, $-O(CH_2)_xO-$, hydroxyalkyl, and alkylaminosulphonylalkyl, where w and x are independently 1 to 4.

9. A compound according to claim 2 of formula (IH)



(IH)

wherein R and R^1 are as defined in relation to formula (I) in claim 1;

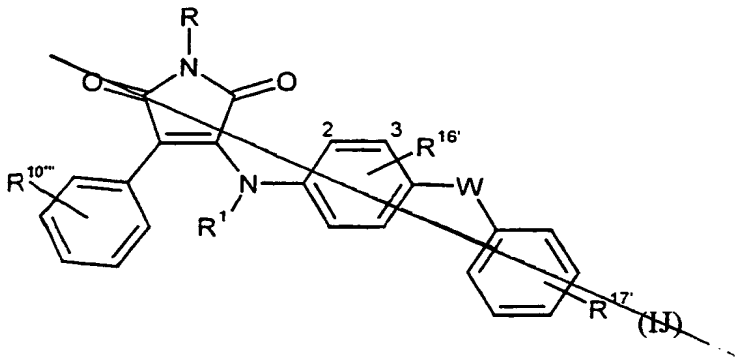
$R^{11'''}$ is $-[(CH_2)_{aa}]-$, where aa is 1 to 4;

$R^{14'}$ is hydrogen;

$R^{15'}$ is alkyl, unsubstituted or substituted phenylamino, unsubstituted or substituted phenylalkylamino, cyclohexylamino, alkenylamino, phenyl, benzyl, styryl, or alkylamino.

10. A compound according to claim 2 of formula (IJ)

contd. a2



(IJ)

wherein R and R^1 are as defined in relation to formula (I) in claim 1;

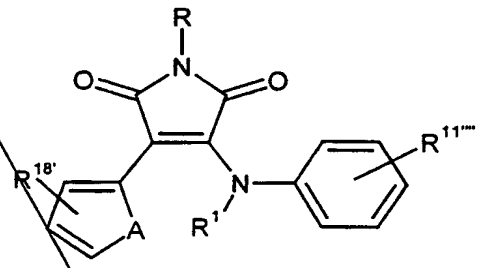
$R^{10'''}$ represents one or more, suitably up to three, substituents independently selected from alkoxy or halo;

$R^{16'}$ represents one or more, suitably up to three, substituents independently selected from hydrogen, carboxy, alkoxycarbonyl, or alkylaminocarbonyl;

$R^{17'}$ represents one or more, suitably up to three, substituents independently selected from carboxy, alkoxycarbonyl, halo, alkylaminocarbonyl, nitro, or hydrogen;

W is sulphur, oxygen, or substituted or unsubstituted NH.

11. A compound according to claim 2 of formula (IK)



(IK)

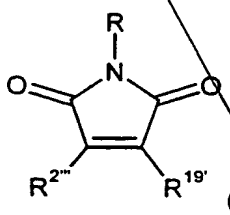
wherein R and R^1 are as defined in relation to formula (I) in claim 1;

$R^{11''''}$ represents one or more, suitably up to three, substituents independently selected from halo and hydroxy;

$R^{18'}$ represents one or more, suitably up to three, substituents independently selected from hydrogen, alkyl, and $-(CH=CH)_2-$;

A is sulphur.

12. A compound according to claim 2 of formula (IL')



(IL')

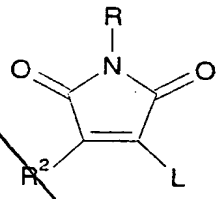
contd. A2

wherein R is as defined in relation to formula (I) in claim 1;

$R^{2'''}$ is unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl;

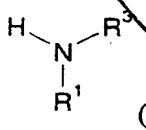
$R^{19'}$ is unsubstituted or substituted heterocyclyl, or a quaternised salt thereof, with the proviso that formula (IL') does not include the compounds contained in List L'.

13. A process for the preparation of a compound of the invention which process comprises reaction of a compound of formula (II):



(II)

wherein R and R^2 are as defined in formula (I) in claim 1 and L is a leaving group, with a compound of formula (III):



(III)

wherein R^1 and R^3 are as defined in formula (I) in claim 1; and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

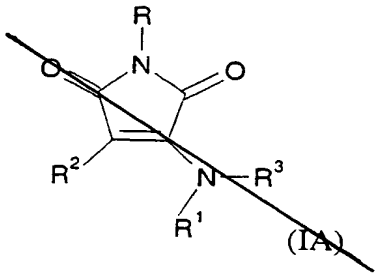
14. A compound of formula (I) according to claim 1 for use in conditions associated with a need for inhibition of glycogen synthase kinase-3.

15. Use of a compound of formula (I) according to claim 1 for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of glycogen synthase kinase-3.

Amen. A3

~~16. A compound of formula (IA)~~

contd. a3



(IA)

wherein

R is hydrogen, alkyl, aryl, or aralkyl;

R^1 is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;

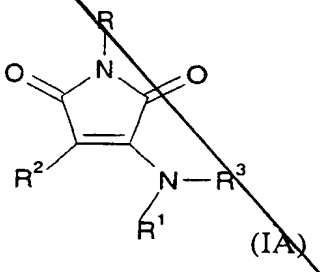
R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;

R^3 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocylic ring;

or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance, with the proviso that formula (IA) does not include the compounds contained in List A.

17. A pharmaceutical composition which comprises a compound of formula (IA)



(IA)

wherein

R is hydrogen, alkyl, aryl, or aralkyl;

R^1 is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;

R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;

R^3 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocylic ring;

or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier, with the proviso that formula (IA) does not include the compounds contained in List A.

18. A method for the treatment and/or prophylaxis of mood disorders in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

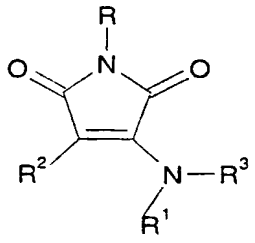
19. A method for the treatment and/or prophylaxis of neurotraumatic diseases in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

20. A method for the treatment and/or prophylaxis of cancer, in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

21. A method for the treatment and/or prophylaxis of hair-loss, in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

22. Use of a GSK-3 inhibitor for the manufacture of a medicament for the treatment and/or prophylaxis of mood disorders, schizophrenia, neurotraumatic diseases, cancer or hair-loss.

23. A compound of formula (I)



(I)

or a derivative thereof, wherein:

R is hydrogen, alkyl, aryl, or aralkyl;

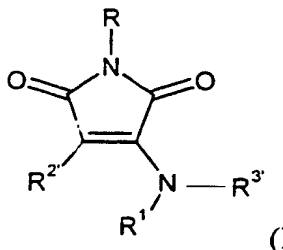
R^1 is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;

R^2 is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;

R^3 is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

R^1 and R^3 together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocylic ring;

with the proviso that the compounds of formula (ID)



(ID)

wherein R and R^1 are as defined in relation to formula (I);

$R^{2'}$ is phenyl, substituted phenyl or indolyl;

$R^{3'}$ is hydrogen, alkyl, cycloalkyl, phenyl, substituted phenyl, C_{1-6} alkylphenyl wherein the phenyl group is optionally substituted, alkoxyalkyl, substituted or unsubstituted heterocyclyl;

are excluded.